PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/008643	11.06.2004	13.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D519/00, A61K31/519, A61P29/00, A61P37/00

Applicant
DAIICHI SUNTORY PHARMA CO., LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/008643

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: EP-A-1 176 147
D2: EP-A-1 092 720
D3: EP-A-0 995 750
D4: US-A-5 541 187

2) Novelty (Reference to section V)

D1 discloses a series of pyrazolo[4,3-d]pyrimidin-7-one compounds of general formula I (cf. page 1 of D1), which differ from compounds of the current application in the absence of the present R^3 group on the pyridinyl-substituent.
The same applies to compounds of D3 (cf. in particular formulas Va and Vb) on page 7 of D3).

D2 describes pyrazolo[4,3-d]pyrimidin-7one-3-pyridylsulphonyl compounds (cf. pages 1-6 of D2), which differ from present compounds in the substituent patten on the pyridine moiety.

D4 refers to 6-heterocyclyl-pyrazolo[3,4-d]pyrimidin-4-ones (cf. formula I on column 4 of D4), over which present compounds of formula IA can be considered a selection (cf. in particular the definition of the group R^6 in D4, which may represent a six membered heterocyclic ring containing one nitrogen and substituted by a 4-morpholinyl group).
However, no compounds are given in D4 falling within the scope of present claim 1.

Thus, the subject-matter of present claims 1-9 meets the requirements of Article 33(2) PCT.

3) Inventive step (Reference to section V)

D4, which may be considered to represent the closest state of the art, discloses 6-heterocyclyl-pyrazolo[3,4-d]pyrimidin-4-ones as inhibitors of the enzymatic activity of phosphodiesterase (PDE). As mentioned above, the subject-matter of current claim 1 consists in a selection over the general formula I of D4.
The problem to be solved by the present application may therefore be considered as the provision of improved phosphodiesterase inhibitors.
The solution proposed by present claim 1 can only be regarded as inventive, if compounds

of present formula (IA) present unexpected effects or properties in relation to those of D4. However, no such effects or properties are indicated in the application.
As regards D1 to D3, it is to be noticed that these documents disclose compounds which are structurally close to those of present formula (IA) and (IB), and which are at the same time PDE inhibitors. The difference between present compounds and those of D1-D3 lies mainly in the position of the current R^3 substituent on the pyridinyl-group, which the skilled person would not deem inventive as the modification of a substituent position would be merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
Furthermore, extremely broad generalisations like "a group which ban be substituted or unsubstituted" are in contradiction with the basis of qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears not to be predictable that all alternatives claimed would achieve the same technical effect.

Consequently, the subject-matter of present claims 1-9 does not meet the criteria of Article 33(3) PCT.

4) Reference to section VII

On page 3, line 1 of the description it has been noticed that the Japanese patent citation is not correct.

5) Clarity (Reference to section VIII)

A certain inconsistency has been noticed between the subject-matter of present claim 1 and example 19 given in the description on page 47, wherein the R^3 group is absent (in claim 1 R^3 can be $-NR^5R^6$, $-C(=O)R^7$ or $S(O)_{0-2}R^8$, while in example 19 R^3 is represented by a hydrogen group).
Thus, the requirements of Article 6 PCT are not met.